DRUG DELIVERY—OPHTHALMIC ROUTE

Massod Chowhan
Alan L. Weiner
Haresh Bhagat
Alcon Research Ltd., Fort Worth, Texas, U.S.A.

INTRODUCTION

Delivery of medication to the human eye is an integral part of medical treatment. The delivery of drug to the site of action has been practiced since ancient times, which successively advanced in a variety of ophthalmic dosage forms. The writings pertaining to eye medications have been found on Egyptian papyri. Between 20 BC and AD 50, Greeks and Romans practiced the delivery of the necessary components of eye medication by dissolving them in water, milk or egg white (1). They used the term *collyria* for such preparations. The term *belladonna* or "beautiful lady" evolved during the middle ages from such collyria, which contained components to dilate the pupils of a lady's eyes for cosmetic purpose (2). The collyria gave rise to the birth of modern-day eye drop solutions.

Prior to World War II and well into the 1940s, most solutions for eye use were compounded by the pharmacist in the community pharmacy and were intended for immediate use, perhaps due to an unconfirmed stability of the drug (2). The availability of such solutions in a sterile dosage form marked the most important milestone in this century for the modern day eye drop solution. Alcon Pharmacy (currently known as Alcon Laboratories Inc.), a dispensing pharmacy during the day and a manufacturing pharmacy during the night, was the first provider of sterile ophthalmic solutions in 1947, long before the Food and Drug Administration (FDA) adopted a position in 1953 that a nonsterile ophthalmic solution was considered adulterated. Subsequently the United States Pharmacopoeia (USP) adopted sterility as requirement for ophthalmic solutions in 1955 (3).

The traditional era of the solution-only dosage form for use in the eye ended in the 1950s with the availability of suspension dosage forms. Solid drug particles of cortisone acetate were first suspended and a suspension product commericialized. In an unorthodox approach, for the first time clinical studies revealed that a sufficiently reduced particle sized drug could be instilled on ocular surfaces. This resulted in the availability of water insoluble or sparingly soluble drugs for the mitigation of ophthalmic disorders in suspension dosage forms.

The successful experimentation of delivering sparingly soluble drugs in a suspended form led the way for products with added values beyond simple presentations. Increasing awareness of basic properties of drug molecules and the wide spread availability of excipients further advanced the discoveries of value added deliveries. Jani et al. (4) reported such delivery of β_1-adrenergic antagonist as a bound drug to cationic polymer resin beads, suspended in an aqueous vehicle. The authors were able to reduce ocular discomfort of betaxolol yet maintain the therapeutic efficacy of the drug for controlling intra ocular pressure.

Gressel et al. (5) reported viscosity modifiers for enhancing intended effects on an ocular surface. A polyacrylic polymer was used to increase viscosity to a gel consistency and thereby enhancing the treatment of symptoms for dry eyes. Sullivan reported efficacy of carbomer gel in improving the number of subjective and objective symptoms of moderate-to-severe dry eye syndromes (6). Such a gel vehicle offered an advantage of reducing frequency of instillation and has resulted in a commercial product (Pilopine HS Gel).

Recognizing the value of rheological properties of polymers facilitated discovery of gel forming solutions for drugs such as timolol maleate. In these systems, timolol is formulated in an aqueous vehicle which on contact with the ocular surface changes to a gel like consistency, thereby, extending the duration of contact. Extending the contact time improved bioavailability thereby reducing the frequency of the dosage to once daily instillation. Two extended duration timolol maleate products, one containing gellan as a gel forming ingredient (Timoptic XE), and the other with xanthan (Timolol Gel Forming Solution) have been approved for commercial use. Shin reported a single daily application of such dosage in reducing intraocular pressure in human subjects (7). Beyond the use of solutions, suspensions and gels, further developments have been made in formulation of creams and ointments, intra-ocular injections, viscoelastic solutions and newer devices and inserts.

EVOLUTION OF OCULAR DRUG DELIVERY SYSTEMS

Topical ocular application of controlled drug delivery systems is a relatively new science compared to earlier ocular dosage form, with roots beginning in the late 1960s to early 1970s.

Delivery of Drugs from Contact Lens Materials

The earliest attempts to significantly prolong the action of drugs applied to the eye focused on using existing systems known in the ophthalmic field. In particular the most well known and characterized solid systems for ocular use are hydrophilic contact lenses. The primary material initially developed for constructing hydrophilic contact lenses was hydroxyethyl methacrylate (HEMA). Many variations of HEMA polymers have since been produced for contact lenses wherein the HEMA is typically copolymerized with methylmethacrylate, ethoxyethylmethacrylate, 1,3-propanediol trimethacrylate, ethylene dimethacrylate, allyl methacrylate, ethylene glycol dimethacrylate, dimethyl oxybutyl acrylamide, or vinyl pyrrolidone. Depending on copolymer composition and cross-linkage, hydrogels of this type range from 38 to 79% water content. Because of this property, it is possible to load polymers of this type with drug by soaking them in an aqueous solution containing the drug. This application was first reported in the early 1970s in papers examining uptake and release of agents such as fluorescein from Bionite lenses produced by Griffin Laboratories and Soflens lenses from Bausch and Lomb. Studies showed significant differences in uptake and release rates for the two types of lenses. Today these results are not unexpected as it has been shown by Sorenson et al. (8) that elimination of radiotracers from presoaked contact lenses are cleared more slowly in lenses containing higher water content and thicker dimensions. In low water content lenses (minimum of 38%), elimination constants of a technetium label were in the range of $0.278-0.155\ \text{min}^{-1}$. In contrast the elimination constant of a 75% hydrated lens was $0.029\ \text{min}^{-1}$, a factor of 7–10 times slower. These differences have been confirmed in other studies using specific drugs such as tobramycin (9).

From an efficacy point of view, early studies with HEMA based lenses were conducted using pilocarpine, the key available glaucoma drug during that era. Several studies reported improvements in reduction of intraocular pressure and corneal drug flux using presoaked lenses containing lower pilocarpine concentrations than standard drops (10–14). In later studies following the identification of timolol as a glaucoma agent (15) it was found that polyvinylmethylmethacrylate circular disks of 13-mm diameter and 0.5-mm thickness will release timolol differentially depending on the addition of a basic additive (disodium phosphate). An enhancement in the rate of release and a shifting of peak timolol levels from 4 h to 30 min were observed when formulated with the additive.

Antibiotics have also been examined for uptake and release from contact lens materials. Impregnation of various hydrogels constructed of various methacrylate and polyvinylpyrrolidone copolymers with erythromycin and erythromycin estolate were effective in slow releasing drug over a period sufficient to suppress *Chlamydia* infection in a monkey model (16, 17). As well, modest increases in intraocular gentamicin have been observed upon administration of gentamicin soaked hydrogel lenses in rabbits (18). Clinically, drug penetration of gentamicin, chloromycetin, or carbenicillin from hydrogel lenses was found to be higher than subconjunctival injection of control solutions over a 2–12-h period posttreatment (19). In prepolymerized poly HEMA minidisks loaded with particles of sulfisoxazole, extended release over a 168-h period was achieved (20). This proved to be successful in treating a *Staphylococcus aureus* infection model in rabbits from one time administration of the minidisk as compared to 3 times daily control solutions.

Absorption and washout characteristics of drugs from poly HEMA based lenses are drug dependent. For example, following a 7-day immersion, increasing levels of uptake are observed for norepinephrine, gentamicin, pilocarpine and dexamethasone, respectively (21). Washout of these drugs from the lens was nearly complete (83–98%). Maximum amounts of these drugs taken up into these lenses represented only one tenth of the dose achievable by application of topical drops. Total uptake of these agents into polymethylmethacrylate was also quite low. These results were supported by earlier studies indicating that intraocular poly HEMA does not act as a significant sponge or long term reservoir for drugs such as dexamethasone, chloramphenicol, epinephrine and pilocarpine (22).

While the majority of reports have examined topical release of drugs from contact lens materials, the implantation of these materials, as is common for intraocular lenses, has been reported. One such example was recorded by Shing et al. (23) who implanted poly HEMA pellets loaded with fibroblast growth factor (FGF)-sucralfate into the cornea as a means to develop a corneal neovascularization model for testing of anti-angiogenic agents. Neovascularization was produced beginning at day 2 and reaching a maximum at day 11 with an elongation rate of 0.41 mm/day until day 13.

Ocusert

At about the same time as investigations were being carried out with contact lens materials for drug release, an ethylene vinyl acetate (EVA) membrane device, Ocusert® was developed by the Alza Corp. (Palo Alto, CA) and eventually commercialized in 1974 (20, 24–28). Ocusert is an elliptical shaped device consisting of two outer layers of rate controlling EVA, and an inner layer of pilocarpine in an alginate gel. The device is designed for continuous release of the drug at a 20 or 40 μg/h rate over 7 days. Enhanced release of the pilocarpine in the higher rate device is facilitated by addition of a flux enhancer, di-(ethylhexyl)phthalate. While this device functions effectively in a specific niche of difficult to manage glaucoma patients, it has not been universally adopted for use because of unsatisfactory control of IOP in some patients, ejection of the device from the eye, and irritation or tolerance difficulties (29–31).

Erodible Polymeric Delivery Systems

During the same period that reports appeared on the Ocusert device, research was progressing on the use of erodible polymer systems for ophthalmic drug delivery. This research blossomed in the early 1980s with a particular focus on polymers employed in the manufacture of absorbable sutures. Release of many ophthalmic drugs from polymeric matrices either via dissolution or erosion was investigated. In addition to the development of slower releasing carrier systems, many papers have since appeared on the use of viscosity additives and bioadhesives to extend retention of delivery systems in the eye. For example albumin nanoparticles containing pilocarpine are better retained by the inclusion of methylcellulose, hydroxpropylmethylcellulose, polyvinylalcohol, sodium carboxymethylcellulose, carbopol 941, hyaluronate or mucin in the formulation (32). Similar effects are noted when carbopol is used in coating ophthalmic gentamicin drug delivery inserts comprised of hydroxypropylcellulose, ethylcellulose, and polyacrylate (33).

Polyvinylalcohol

Polyvinylalcohol disks for delivery of drugs to the eye were proposed as early as 1966 for potential use by astronauts (34). Pilocarpine loaded disks exhibited sustained miosis and IOP reduction in human subjects. Maichuk (35–37) has elaborated on these early studies by showing that PVA films containing pilocarpine, antibiotics, or antimetabolites increased drug concentration in the tear film and prolonged the delivery times. Similarly, bioavailability, miotic activity in rabbits, and intraocular pressure control in human glaucoma subjects were all enhanced over a 24-h period with PVA/pilocarpine–PAA disks of 4-mm diameter and 0.4-mm thickness prepared from cast films (38). A PVA film device termed NODS ("new ophthalmic delivery system") has also been utilized for studying improvement in delivery of pilocarpine, tropicamide, chloramphenicol, and proparacaine (39). Heat-treated PVA membrane sandwiches have been prepared with 5 mg of ganciclovir, which released at a rate of 0.25 $\mu g/h/mm^2$ over a 1-week period (40). Similarly, pellets of either thalidomide (41), cyclosporin (42), or leflunomide (43) with either PVA incorporated into the pellet or coating the pellet have exhibited sustained release of those drugs either in vitro or in the vitreous or subconjunctival spaces.

Delivery of drugs from collagen shields

The concept of drug delivery from contact lenses was extended to include contact lens-shaped collagen shields after their approval for use directly on the surface of the eye to treat corneal wounds (44–46). Several types of collagen shields are commercially available under such names of ProShield (Alcon Laboratories, Inc., Fort Worth, TX), Bio-Cor (Bausch & Lomb, Clearwater, FL), and Soft Shield (Oasis, Glendora, CA). The collagen for these products is derived from a bovine or porcine source with dimensions of 14.5 mm in diameter and thickness between 0.012 and 0.071 mm. In the eye these shields dissolve over a 12–72 h period depending on the amount of cross-linkage. Similar to the earlier contact lens studies, the majority of investigations examining release of active agents from collagen matrices first involve loading of active agent into the shield by soaking in the agent over a sufficient period of time (47). Because of the relatively large pore size, diffusion into and out of the shield does not typically surpass 2–3 h.

Many studies have looked into prolongation of aminoglycoside antibiotic release from collagen matrices. Tear film and topical tissue levels (sclera and cornea) of gentamicin delivered from collagen matrices is elevated over controls as determined by pharmacokinetic evaluation of 14C-gentamicin (48). In models of *Pseudomonas keratitis* in rabbits (49, 50), collagen shields loaded with gentamicin (49, 50) or tobramycin (51) have produced significant reductions in colony-forming units (CFU) over control animals given drug alone. However, changing from the shield design to either a doughnut (52) or disk (53) does not seem to offer an improvement in gentamicin release. Although aqueous humor levels of gentamicin are not achieved when using shields presoaked in 40 mg/ml gentamicin as compared to drops (54), levels of tobramycin delivered from shields

have been detected in aqueous humor (55, 56). Neither repetitive drop treatment nor release from collagen shields results in the establishment of vitreous drug levels. More extensive studies have been reported on collagen shields to deliver tobramycin (57–62) in various other tests of ocular trauma. Enhanced delivery of procaine penicillin, erythromycin, erythromycin estolate (63), silver nitrate 1%, povidone-iodine 5%, chlorhexidine gluconate 1% (64), and amphotericin 5% (65) from collagen shields also has been reported.

Similar to antibiotic studies, delivery of corticosteroids from collagen shields has been demonstrated to produce prolongation of effects, enhanced penetration, and increased efficacy (66–69).

Antimetabolites such as 5-fluorouracil (5-FU) have been used experimentally for retarding the healing of incisions made to improve outflow of aqueous humor and reduction in intraocular pressure in glaucoma patients. Several groups have examined the potential of 5-FU loaded collagen shields for improving current therapy over 5-FU alone (10, 71–73). Increases in duration of action and success rates have been noted. Another antimetabolite, trifluorothymidine, when released from collagen shields was investigated as a potential treatment for ulcerative herpetic keratitis (74). In these studies, cornea and aqueous humor levels were 19–42% higher when eyes were treated with drug loaded shields.

More effective treatment of glaucoma has also been attempted using collagen shield technology. In this regard, shields have been shown to prolong delivery of pilocarpine (75–77) and metipranolol (78).

Collagen disks have had their greatest application in the treatment of wounds. Enhancement of the inherent protective property of the material has been investigated with the subsequent inclusion of growth factors. Collagen disks soaked for 5 min in platelet derived or epidermal growth factors (100 μg/ml) was capable of increasing the wound healing rates of debrided corneas in rabbits (79). Following placement on the cornea, collagen shields containing tissue plasminogen activator shortened fibrin clot lysis time by 50% over controls (80). Another wound modulator, cyclosporin A delivered by topical collagen shields, has been reported to be 10-fold higher in cornea and aqueous humor over an 8-h period as compared to controls (81).

Polylactide (PLA), polyglycolide (PGA) and polycaprolactone (PCL)

A further extension of drug delivery using naturally biodegrading materials other than collagen included the application of known eroding suture materials. Polylactic acid, polyglycolic acid and polycaprolactone are the primary materials used in dissolvable sutures including Dexon® (Davis and Geck, Danbury, CT) and Vicryl® Polyglactin (Ethicon, Somerville, NJ). The key focus of ocular drug delivery from these polymers has been for sustained release of 5-FU. Sustained release 5-FU from PLA/PGA copolymer microspheres had been utilized for applications in glaucoma filtration surgery and proliferative vitreoretinopathy (82–86). Release of 5-FU is controllable over a 7-day period in vitro and when injected into the vitreous PLA microspheres (with 2 mg drug) degrades over a 48-day period. In a PVR model, tractional retinal detachments are reduced from 60 to 10% of animals when 1.25 mg of drug is delivered from PLA microspheres as compared to control injections (83). In animals, vitreous concentrations of 5-FU delivered from PLA/PGA microspheres (250 μg) or rods (1 mg) can be detected from periods between 11 days (87) and 21 days (88–90). PLA/PGA devices incorporating 5-FU prevented retinal detachments in an experimental model that was not responsive to drug alone. PLA/PGA disks containing 5-FU are also efficacious for periods greater than one month in applications for glaucoma filtration surgery (91, 92). Devices of this type have shown some inflammatory and vascularization reactions depending on site of implantation (90, 93). PLA microspheres have shown sustained efficacy in delivering other antimetabolites such as doxorubicin (94, 95).

PLA, PGA and PCL delivery systems have also proven to be of value in delivering glaucoma agents. Nanoparticles (150-nm diameter) and nanocapsules (300-nm diameter) constructed from polycaprolactone incorporating either 1% carteolol chlorhydrate or 0.5% betaxolol were shown to be more effective than controls in hypertension models (96, 97). Prolongation of miosis has also been observed in rabbits receiving microcapsules constructed from PLA and containing pilocarpine hydrochloride (98).

Anti-inflammatory and anti-infective agents such as indomethacin, fluconazole, and dexamethasone have been incorporated into PLA, PLG, or PCL carriers (99–101). Significant increases in either drug concentration or duration of action were noted.

Polyanhydrides, polyorthoesters, and polyalkylcyanoacrylates

Beyond the use of suture materials, newer erodible polymeric materials were introduced in the 1980s as potential ophthalmic carrier systems for release of drugs.

As with PLA or PLG carriers, the application of either polyanhydride or polyorthoester polymers for 5-FU sustained release in glaucoma treatment or PVR has been investigated (102–107). Using compression

techniques, polyanhydride devices constructed from combinations of (*p*-carboxyphenoxy)alkanes with sebacic acid have been produced. Disk or T-shaped polyanhydride devices containing between 10 and 20% 5-FU prolonged IOP reduction and bleb survival in filtration models or better inhibited tractional retinal detachments in PVR models than standard drug controls. Similar effects on extended filtration bleb survival and IOP reduction have been observed for polyanhydride implants containing daunorubicin (108) or mitomycin C (109). Release of drugs from polyanhydride implants have been examined when administered subconjunctivally (etoposide) (110) or in the vitreous or anterior chamber (gentamicin) (111). In these reports slow release rates were established at least over a 1-week period. In context of vitreous delivery, polyorthoesters have been shown to release ganciclovir for 144 h which is controllable by the pH of the dissolution media (112).

Ocular distribution and elimination of biodegradable polyalkylcyanoacrylate nanoparticles has been examined in a number of reports (113–117). Pilocarpine containing polybutylcyanoacrylate nanoparticles alone or in gel type formulations are capable of enhancing and prolonging the miosis and pressure lowering response in various animal models (118–122).

Non-erodible Systems

Distinct from the development of contact lens materials or the Ocusert in the 1970s, additional promising delivery systems and materials have emerged with the more recent focus on development of intraocular applications for treatment of macular degeneration, cataract, retinopathy, and inflammation.

Vitrasert®

The Vitrasert, approved in 1996 and currently marketed by Bausch and Lomb is an ethylene vinyl acetate cup encasing a cylindrical core of ganciclovir, which is covered on one or two surfaces with a permeable PVA membrane to allow for diffusion (123–134). At the base of the cup is an anchoring strut made of PVA to allow for suturing. The drug core diameter of the device is 2.5 mm. Sustained levels of the drug are maintained in the vitreous over a period of 6–8 months in the treatment for cytomegalovirus (CMV) induced retinitis. This device has also been investigated for the delivery of 5-FU (126–130), flurbiprofen (131) cyclosporin (132), dorzolamide (133), and dexamethasone (134) when implanted at various sites. A variation on this device has been constructed using a core of ganciclovir/polylactide-glycolide encased in a crosslinked poly[HEMA-co(PVA-AA)] film that releases the drug in the vitreous over 63 days (135).

Silicones

Ophthalmic practice has long employed silicone polymers in surgeries utilizing scleral buckles and sponges, retinal tamponade and foldable intraocular lenses. Silicone elastomers and rubbers are hydrophobic in nature and therefore support long term payout characteristics for many drugs. Silicone polymer disks of 4–5-mm diameter termed minidiscs have been studied for the release of gentamicin when placed in the conjunctival cul-de-sac (20, 136). Slow release of the drug is observed over a period of 10–14 days with tear concentrations in the range of 2.5 ppm during this period. Nanoparticles of silicone in the 150–200 μm size range can be made and when containing timolol effectively prolonged release of the drug (137). Sealed silicone tubes 1.46 mm ID by 15 mm length and filled with 2.5–20 mg/ml solutions of timolol slow release the drug over 8 h in vitro (138) or in vivo (139). Recently, development of a solid noodle-like silicone controlled drug delivery rod for the deep cul-de-sac (fornix) known as the Ocufit SR® has been reported (140–143). These rods have been shown to slow release oxytetracycline or diclofenac over several weeks and have shown good wear compliance in humans (144, 145). Liquid silicone can also be used as a surface coat in developing delivery devices. This approach has been reported for polydimethylsiloxane coated solid drug implants that are used to enhance sustained delivery in the eye (41, 42).

CONCLUSIONS

Efficacious delivery of drugs in the eye is dependent on a host of factors including activity at the receptor, absorption and penetration of the drug for the site of application, clearance rates from the biological compartment, delivery rate and duration of the drug from the site of application, toxicology of the total dosage form, and patient compliance with the dosage form. The evolution of acceptable systems as drug carriers in the eye is usually influenced simultaneously by several of these factors. Solution or suspension drops and ointments still remain the first line approach to treatment in standard therapies. However, in circumstances demanding less frequent dosing, or dosing into less accessible compartments of the eye, more unique approaches are indicated. In those cases, use of gelling, eroding or non-eroding polymer systems has proven to be of significant value.

REFERENCES

1. Olejnik, O. Conventional Systems in Ophthalmic Drug Delivery. *Ophthalmic Drug Delivery Systems*; Mitra, A.K. Ed.; Marcel Dekker, Inc.: New York, 1993; 177–198.
2. King, R.E. *Dispensing of Medication*, 9th Ed. Mack Publishing Co.
3. USP Pharmacopeia. *United States Pharmacopeial Convention, Inc.*: Rockville MD, 1995.
4. Jani, R.; Gan, O.; Ali, Y.; Rodstrom, R.; Hancock, S. J. Ocul. Pharmacol. **1994**, *10*, 57.
5. Gressel, P.D.; Roehrs, R.E., US Patent 5,075,104, 1991.
6. Sullivan, K.J.; McCurrach, F.; Lee, S.; Taylor, H.R.; Rolando, M.; Marechal-Courtois, C.; Creuzot, G.C.; East, D.L.; Karabatsas, C.; Bingh-Hoh, M.; Faschinger, C.; Laroche, L. Ophthamol. **1997**, *104*, 140.
7. Hosaka, S.; Ozawa, H.; Tanzawa, H.; Kinitomo, T.; Nichols, R.L. Vivo Evaluation of Ocular Inserts of Hydrogel Impregnated with Antibiotics for Trachoma Therapy Basic Research Laboratories and the Department of Microbiology Harvard School of Public Health, 1982.
8. Soronson, T.B. Acta Ophthalmol. **1984**, *167* (Suppl.), 1.
9. Matoba, A.Y.; McCulley, J.P. Ophthalmol., **1985**, *92*, 97.
10. North, D.P. Can. Med. Assoc. J. **1971**, *105*, 561.
11. Podos, S.M.; Becker, B.; Assoff, C. Am. J. Ophthalmol., **1972**, *73*, 336.
12. Kaufman, H.E.; Uotila, M.H.; Gasset, A.R.; Wood, T.O.; Ellison, E.D. Trans. Am. Acad. Ophthalmol. Otolaryngol**.** **1971**, *75*, 361.
13. Krohn, D.L. Trans. Am. Ophthalmol. Soc. **1978**, *76*, 502.
14. Krohn, D.L.; Breitfeller, J.M. Invest. Ophthalmol. **1975**, *14*, 152.
15. Urtti, A.; Kyyrönen, K.; Finne, U.; Vartianinen, E.; Väisänen, V. Proc. Int. Symp. Contr. Rel. Bioact. Mat. **1990**, *17*, 472.
16. Ozawa, H.; Hosaka, S.; Kunitomo, T.; Tanzawa, H. Biomaterials **1983**, *4*, 170.
17. Hosaka, S.; Ozawa, H.; Tanzawa, H.; T Kunitomo; Nichols, R.L. Biomaterials **1983**, *4*, 243.
18. Mester, U.; Krasemann, C.; Stein, H.J. Klin. Monstsbl. Augenheilkd **1976**, *169*, 492.
19. Jain, M.R. Br. J. Ophthalmol. **1988**, *72*, 150.
20. Bawa, R. *Ophthalmic Drug Delivery Systems*; Mitra, A.K. Ed.; Marcel Dekker, Inc.: New York, 1993, 223.
21. Chapman, J.M.; Cheeks, L.; Green, K. J. Cataract Refract. Surg. **1992**, *18*, 456, 9.
22. Heyman, T.P.; McDermott, M.L.; Ubels, J.L.; Edelhauser, H.F. J. Cataract Refract. Surg. **1989**, *15*, 169.
23. Shing, Y.; Gonzales, E.M.; Li, W.W.; Casey, R.; Panigrahy, D.; Folkman, J. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1992**, *33*, 1027.
24. Baker, R.; Lonsdale, H. Chem. Technol. **1975**, *5*, 668.
25. Urquhart, J. *Ophthalmic Drug Delivery System*; Robinson, J.R., Ed.; American Pharmaceutical Association: Washington, DC, 1980; 105.
26. Shell, J.W. Ophthalmic Surg. **1974**, *5*, 73.
27. Chien, Y.W. *Novel Drug Delivery Systems*; Ch. 2 Marcel Dekker, Inc.: New York, 1982; 13.
28. Friederich, R.L. Ann. Ophthalmol. **1974**, *6*, 1279.
29. Sihvola, P.; Puustjarvi, T. Acta Ophthalmol. **1980**, *58*, 933.
30. Akerblom, T.; Aurell, E.; Cristiansson, J.; Kriisa-Kunnos, V.; Wiebert, O. Acta Ophthalmol., **1980**, *58*, 617.
31. Pollack, I.P.; Quigley, H.A.; Harbin, T.S. South Med. J. **1976**, *69*, 1296–9.
32. Zimmer, A.K.; Chetoni, P.; Saettone, M.F.; Zerbe, H.; Kreute, J. J. Contr. Rel. **1995**, *33*, 31.
33. Gurtler, F.; Kaltsatos, V.; Boisrame, B.; Gurny, R. J. Contr. Rel. **1995**, *33*, 231.
34. Yakovlev, A.A.; Lenkevich, M.M. Vestn. Ophthalmol. **1966**, *79*, 40.
35. Maichuk, Y.F. Antibiotiki **1967**, *5*, 435.
36. Maichuk, Y.F. Invest. Ophthalmol. **1975**, *14*, 87.
37. Maichuk, Y.F. Lancet 1 **1975**, *173.*
38. Saettone, M.F.; Giannaccini, B.; Chetoni, P.; Galli, G.; Chiellini, E. J. Pharm. Pharmacol. **1984**, *36*, 229.
39. Richardson, M.C.; Bentley, P.H. *Ophthalmic Drug Delivery Systems*; Mitra, A.K., Ed.; Marcel Dekker, Inc.: New York, 1993; 355.
40. Pearson, P.A.; Hollins, J.C.; Baldwin, L.B.; Smith, T.J. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1989**, *30*, 511.
41. Velez, G.; Robinson, M.R.; Durbin, T.; Yuan, P.; Sung, C.; Whitcup, S.M. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1999**, *40*, 584.
42. Robinson, M.R.; Yuan, P.; Gogolak, L.; Tansey, G.; Smith, J.; Whitcup, S.M. ARVO Abstract. Invest. Ophthalmol., **1999**, *40*, S84.
43. Gogolak, L.; Robinson, M.R.; Yuan, P.; Aghera, A.; Sung, C.; Whitcup, S.M. ARVO Abstract. Invest. Ophthalmol. **1999**, *40*, S85.
44. Mondino, B.J. Am. J. Ophthalmol., **1991**, *112*, 587.
45. Robin, J.B.; Keys, C.L.; Kaminski, L.A.; Viana, M.A. Invest. Ophthalmol. Vis. Sci. **1990**, *31*, 1294.
46. Harrison, K.W. J. Ophthalmic Nurs. Technol. **1989**, *8*, 97.
47. Fridberg, M.L.; Pleyer, U.; Mondino, B.J. Ophthalmol. **1991**, *98*, 725.
48. Bloomfield, S.E.; Miyata, T.; Dunn, M.W.; Bueser, N.; Stenzel, K.H.; Rubin, A.L. Arch. Ophthalmol. **1978**, *96*, 885.
49. Silbiger, J.; Stern, G.A. Ophthalmol. **1992**, *99*, 889.
50. Brockman, E.B.; Hobden, J.A.; Hill, J.M.; O'Callaghan, J.; Reidy, J.J.; Insler, M.S.; Kaufman, H.E. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1990**, *31*, 558.
51. Hobden, J.A.; Reidy, J.J.; O'Callaghan, R.J.; Hill, J.M.; Insler, M.; Rootman, D. Arch. Ophthalmol. **1988**, *106*, 1605.
52. Foster, J.A.; Robin, J.B.; Shipplett, C.; Viana, M.; Foster, F.J. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 1291.
53. Liang, F.-Q.; Viola, R.S.; Nakada, S.; del Cerro, M.; Aquavella, J.V. Invest. Ophthalmol. Vis. Sci. **1992**, *33*, 2194.
54. Baziuk, N.; Gremillion, C.M.; Peyman, G.A.; Cho, H.K. Int. Ophthalmol. **1992**, *16*, 101.
55. Unterman, S.R.; Rootman, D.S.; Hill, J.M.; Parelman, J.J.; Thompson, H.W.; Kaufman, H.E. J. Cataract Refract. Surg. **1988**, *14*, 500.
56. Duzman, E.; Chen, C.C.; Takruri, H. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 1291.
57. Sawusch, M.R.; O'Brien, T.P.; Dick, J.D. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1988**, *29*, 228.
58. O'Brien, T.P.; Sawusch, J.D.; Hamburg, T.R. J. Cataract Refract. Surg. **1988**, *14*, 505.

59. Shofner, R.S.; Kaufman, H.E.; Hill, J.M. Ophthalmol. Clin. North Amer. **1989**, *2*, 15.
60. Unterman, S.R.; Rootman, D.S.; Hill, J.M.; Kaufman, H.E. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1988**, *29*, 52.
61. Poland, D.E.; Kaufman, H.E. J. Cataract Refract. Surg. **1988**, *14*, 489.
62. Assil, K.K.; Zarnegar, S.R.; Fouraker, B.D.; Schanzlin, D.J. Amer. J. Ophthalmol., **1992**, *113*, 418.
63. Punch, P.I.; Costa, N.D.; Edwards, M.E.; Wilcox, G.E. J. Vet. Pharmacol. Ther. **1987**, *10*, 37.
64. Esswein, M.B.; O'Brien, T.P.; Osato, M.S.; Jones, D.B. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1990**, *31*, 452.
65. Schwartz, S.D.; Harrison, S.A.; Engstrom, R.E.; Bowden, R.E.; Lee, D.A.; Mondino, B.J. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1990**, *31*, 558.
66. Hwang, D.G.; Stern, W.H.; Hwang, P.H.; MacGowan-Smith, L.A. Arch. Ophthalmol. **1989**, *107*, 1375.
67. Hwang, D.G.; Stern, W.H.; Alyeat, E.B.; MacGowan-Smith, L.A. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1989**, *30*, 248.
68. Aquavella, J.V.; Ruffini, J.J.; LoCascio, J.A. J. Cataract Refract. Surg. **1988**, *14*, 492.
69. Sawusch, M.R.; O'Brien, T.P.; Updegraff, S.A.; Gottsch, J.D. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1989**, *30*, 479.
70. Finkelstein, I.; Trope, G.E.; Menon, I.A.; Rootman, D.S.; Basu, P.K. Curr. Eye Res. **1990**, *9*, 653.
71. Finkelstein, I.; Trope, G.E.; Menon, I.A.; Spero, L.; Rootman, D.S.; Heathcoat, J.F. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1990**, *31*, 591.
72. Sachdev, S.; Zou, X.; Higgenbothan, E. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1990**, *31*, 3.
73. Hasty, B.; Hever, D.K.; Minckler, D.S. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1989**, *30*, 418.
74. Gussler, J.R.; Ashton, P.; VanMeeter, W.S.; Smith, T.J. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1990**, *31*, 485.
75. Laucuta, S.E. Int. J. Pharmaceut. **1989**, *54*, 71.
76. Kitazawa, Y. Acta Soc. Ophthalmol. Jpn. **1975**, *79*, 1715.
77. Vasantha, R.; Sehgal, P.K.; Panduranga Rao, K. Int. J. Pharm. **1988**, *47*, 95.
78. Ball, S.; Badeaux, J.; Graham, M.; Balazy, M.; Bazan, N.G. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1990**, *31*, 405.
79. Nakada, S.; Viola, R.S.; Aquavella, J.V. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 1292.
80. Murray, T.G.; Jaffe, G.J.; McKay, B.S.; Han, D.P.; Burke, J.M.; Abrams, G.W. Refract. Corneal Surg. **1992**, *8*, 44.
81. Reidy, J.J.; Gebhardt, B.M.; Kaufman, H.E. Cornea **1990**.
82. Moritera, T.; Ogura, Y.; Arai, M.; Honda, Y.; Wada, R.; Hyon, S.-H.; Ikada, Y. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1989**, *30*, 249.
83. Moritera, T.; Ogura, Y.; Yoshimura, N.; Honda, R.; Wada, R.; Hyon, S.-H.; Ikada, Y. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1990**, *31*, 384.
84. Moritera, T.; Ogura, Y.; Yoshimura, N.; Kuriyama, S.; Nakano, T.; Honda, Y.; Tabata, Y.; Ikada, Y. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 1294.
85. Moritera, T.; Ogura, Y.; Kimura, H.; Misumi, C.; Takeuchi, A.; Honda, Y.; Ikada, Y. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1992**, *33*, 1012.
86. Moritera, T.; Ogura, Y.; Honda, Y.; Wada, R.; Hyon, S.-H.; Ikada, Y. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 1785.
87. Peyman, G.A.; Conway, M.; Khoobehi, B.; Soike, K. Int. Ophthalmol. **1992**, *16*, 109.
88. Davis, P.A.; Kiss, K.; Parrish, R.K.; Villain, F.; Parel, J.-M.; Cousins, S.W. Proc. Int. Symp. Contr. Rel. Bioact. Mat. **1992**, *19*, 339.
89. Rubsamen, P.F.; Davis, P.; Hernandez, E.; Parel, J.-M.; Cousins, S.W. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1992**, *33*, 728–737.
90. Portugal, L.; Parel, J.-M.; Parrish, R.; Bichon, D. Proc. Int. Symp. Contr. Rel. Bioact. Mat. **1989**, *16*, 105.
91. Sheardown, H.; Chiu, L.-K.; Chiu, W.-J.; Trope, G.E.; Cheng, Y.-L.; Rootman, D.S.; Gould, L.; Liu, G.S. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1992**, *33*, 1390.
92. Gould, L.; Trope, G.E.; Morrison, H.; Cheng, Y.-L.; Rootman, D.S.; Heathcoat, G.; Menon, I.A.; Rootman, D.S.; Liu, G.S.; Chiu, L.-K.; Basu, P.K.; Lyn, W. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 1122.
93. Khoobehi, B.; Stradtmann, M.O.; Peyman, G.A.; Aly, O.M. Ophthalm. Surg. **1990**, *21*, 840.
94. Moritera, T.; Ogura, Y.; Yoshimura, N.; Honda, Y.; Wada, R.; Hyon, S.-H.; Ikada, Y. Invest. Ophthalmol. Vis. Sci. **1992**, *33*, 3125.
95. Kimura, H.; Ogura, Y.; Moritera, T.; Honda, Y.; Wada, R.; Hyon, S.-H.; Ikada, Y. Invest. Ophthalmol. Vis. Sci. **1992**, *33*, 3436.
96. Maincent, P.; Marchal-Heussler, L.; Sirbat, D.; Thouvenot, P.; Hoffman, M.; Vallet, J.A. Proc. Int. Symp. Contr. Rel. Bioact. Mat. **1992**, *19*, 226.
97. Marchal-Heussler, L.; Sirbat, D.; Hoffman, M.; Maincent, P. Pharm. Res. **1992**, *10*, 386.
98. Vidmar, V.; Pepeljnjak, S.; Jalsenjak, I. Microencapsul. J. **1985**, *2*, 289.
99. Masson, V.; Billardon, P.; Fessi, H.; Devissaguet, J.P.; Puisieux, P. Proc. Int. Symp. Contr. Rel. Bioact. Mat. **1992**, *19*, 423.
100. Kimura, H.; Ogura, Y.; Moritera, T.; Honda, Y.; Hyon, S.-H.; Ikada, Y. Invest. Ophthalmol. Vis. Sci. **1992**, *33*, 1013.
101. Herrero-Vanrell, R.; Alvarez-Santiago, C.; Barcia, E. Invest. Ophthalmol. **1999**, *40*, S84.
102. Lee, D.A.; Leong, K.W.; Panek, W.C.; Eng, C.T.; Glasgow, B.J. Invest. Ophthalmol. Vis. Sci. **1988**, *29*, 1692.
103. Lee, D.A.; Flores, R.A.; Anderson, P.J.; Leong, K.W.; Teekhasaenee, C.; DeKater, A.W.; Hertzmark, E. Ophthalmol. **1987**, *94*, 1523.
104. Jampel, H.D.; Leong, K.W.; Dunkelberger, G.; Quigley, H. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1989**, *30*, 417.
105. Lewis, H.; Schwartz, S.; Lee, D.A.; Leong, K.W. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 1047.
106. Alonso, J.I.; Pastor, J.C.; Lopez, I.; Mate, A.; Mateu, C.; Aberola, A.; Sañudo, C. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 1293.
107. Tabatabay, C.; Einmahl, S.; Behar-Cohen, F.; Gurny, R. Invest. Ophthalmol. **1999**, *40*, S84.
108. Dukes, A.J.; Rabowsky, J.H.; Lee, D.A.; Leong, K.W. ARVO Abstract. Invest. Ophthalmol Vis. Sci. **1992**, *33*, 1391.
109. Charles, J.B.; Ganthier, R. Jr; Wilson, M.R.; Lee, D.A.; Baker, R.S.; Leong, K.W.; Glasgow, B.J. Ophthalmol. **1991**, *98*, 503.

110. Koya, P.; Jampel, H.; Quigley, H.; Leong, K.W. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 745.
111. Merkli, A.; Wüthrich, P.; Heller, J.; Tabatabay, C.; Gurny, R. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1992**, *33*, 1392.
112. Gaynon, M.; Heller, J.; Wüthrich, P. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 883.
113. Wood, R.W.; Li, V.H.K.; Kreuter, J.; Robinson, J.R. Int. J. Pharm. **1985**, *23*, 175.
114. Diepold, R.; Kreuter, J.; Guggenbuhl, P.; Robinson, J.R. Int. J. Pharm. **1989**, *54*, 149.
115. Li, V.H.; Wood, R.W.; Kreuter, J.; Hamia, T.; Robinson, J.R. Microencapsul. J. **1986**, *3*, 213.
116. Zimmer, A.; Kreuter, J.; Robinson, J.R. Microencapsul. J. **1991**, *8*, 497.
117. Das, S.K.; Tucker, I.G.; Davies, N.M. Proc. Int. Symp. Contr. Rel. Bioact. Mat. **1992**, *19*, 395.
118. Harmia, T.; Speiser, P.; Kreuter, J. J. Microencapsul. **1986**, *3*, 3.
119. Harmia, T.; Kreuter, J.; Speiser, P.; Boye, T.; Gruny, R.; Kubis, A. Int. J. Pharm. **1986**, *33*, 187.
120. Diepold, R.; Kreuter, J.; Himber, J.; Gurny, R.; Lee, V.H.K.; Robinson, J.R.; Saettone, M.F.; Schnaudigel, O.E. Greafe's Arch. Clin. Exp. Ophthalmol. **1989**, *227*, 188.
121. Cheeks, L.; Green, K.; Stone, R.P.; Riedhammer, T. Curr. Eye Res. **1989**, *8*, 1251.
122. Desai, S.D.; Blanchard, J. S-200 Abstract PDD 7125. Pharm. Res. 9 **1992**.
123. Goins, K.M.; Blandford, D.L.; Pearson, P.A.; Schmeisser, E.; Hollins, J.C.; Smith, T.J. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1990**, *31*, 364.
124. Smith, T.J.; Pearson, P.A.; Blandford, D.L.; Brown, J.D.; Goins, K.A.; Hollins, J.L.; Schmeisser, E.T.; Glavinos, P.; Baldwin, L.B.; Ashton, P.A. Arch. Ophthalmol. **1992**, *110*, 255.
125. Sanborn, G.E.; Anand, R.; Torti, R.E.; Nightingale, S.D.; Cal, S.X.; Yates, B.; Ashton, P.; Smith, T.J. Arch. Ophthalmol. **1992**, *110*, 188.
126. Baldwin, L.B.; Pearson, P.A.; Smith, T.J. Proc. Int. Symp. Contr. Rel. Bioact. Mat. **1990**, *17*, 417.
127. Blandford, D.L.; Smith, T.J.; Brown, J.D.; Pearson, P.A.; Ashton, P. Invest. Ophthalmol. Vis. Sci. **1992**, *33*, 3430.
128. Smith, T.J.; Dharma, S.; Rafii, M.; Ashton, P. ARVO, Invest. Abstract. Ophthalmol. Vis. Sci. **1992**, *33*, 737.
129. Pearson, P.A.; Solomon, K.D.; Van Meter, W.S.; Smith, T.J.; Ashton, P. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 797.
130. Amrien-Noll, J.; Brown, J.D.; Ashton, P.; Conklin, J.; Gussler, J.; Smith, T.J.; Hollins, J.C. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1991**, *32*, 797.
131. Hainsworth, D.P.; Rafii, M.; Conklin, J.D.; Ashton, P. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1993**, *34*, 1491.
132. Pearson, P.A.; Jaffe, G.J.; Martin, D.F.; Ashton, P. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1993**, *34*, 1492.
133. Rafii, M.; Blandford, D.L.; Ashton, P. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1993**, *34*, 1492.
134. Baker, C.W.; Hainsworth, D.P.; Conklin, J.D.; Ashton, P. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1993**, *34*, 1492.
135. Yang, D.C.S.; Wang, Y.J.; Chang, W.C.; Wang, W.W.; Liu, J.H. Invest. Ophthalmol. **1999**, *40*, S87.
136. Bawa, R.; Nandu, M.; Downie, W.; Robinson, J.R. Proc. Int. Symp. Contr. Rel. Bioact. Mat. **1989**, *16*, 213.
137. Sutinen, R.; Laasanen, V.; Paronen, P.; Urtti, A. J. Contr. Rel. **1995**, *33*, 163.
138. Urtti, A.; Pipkin, J.D.; Rork, G.; Repta, A.J. Int. J. Pharm. **1990**, *61*, 235.
139. Urtti, A.; Pipkin, J.D.; Rork, G.; Sendo, T.; Finne, U.; Repta, A.J. Int. J. Pharm. **1990**, *61*, 241.
140. Darougar, S. US Patent 5, 147,647, 1992.
141. Weiner, A.L.; Darougar, S.; Siddque, M.; Raul, V. ARVO Abstract. Invest. Ophthalmol. Vis. Sci. **1993**, *34*, 1489.
142. Weiner, A.L.; Darougar, S.; Siddque, M.; Raul, V. Proc. Int. Symp. Contr. Rel. Bioact. Mat. Abstract **1993**, *20*, 1222.
143. Darougar, S.; Weiner, A.L. US Patent 5,322,691, 1994.
144. Peiffer, R.L.; Osborne, C.M.; Smith, P.C.; Wang, C.; Weiner, A.L. Invest. Ophthalmol. **1995**, *36*, S1021.
145. Hubbell, H.R.; Noonan, J.S.; Lee, S.B.; Swaminathan, A.; Kaminski, E.A.; Edelhauser, H.F. Invest. Ophthalmol. **1999**, *40*, S85.